# *“SLE: Fighting Self Sabotage”*

**BY**

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**INTERNAL MEDICINE**

**RHEUMATOLOGY & IMMUNOLOGY**

# *Objectives*

**I. Epidemiology**

**II. Pathogenesis**

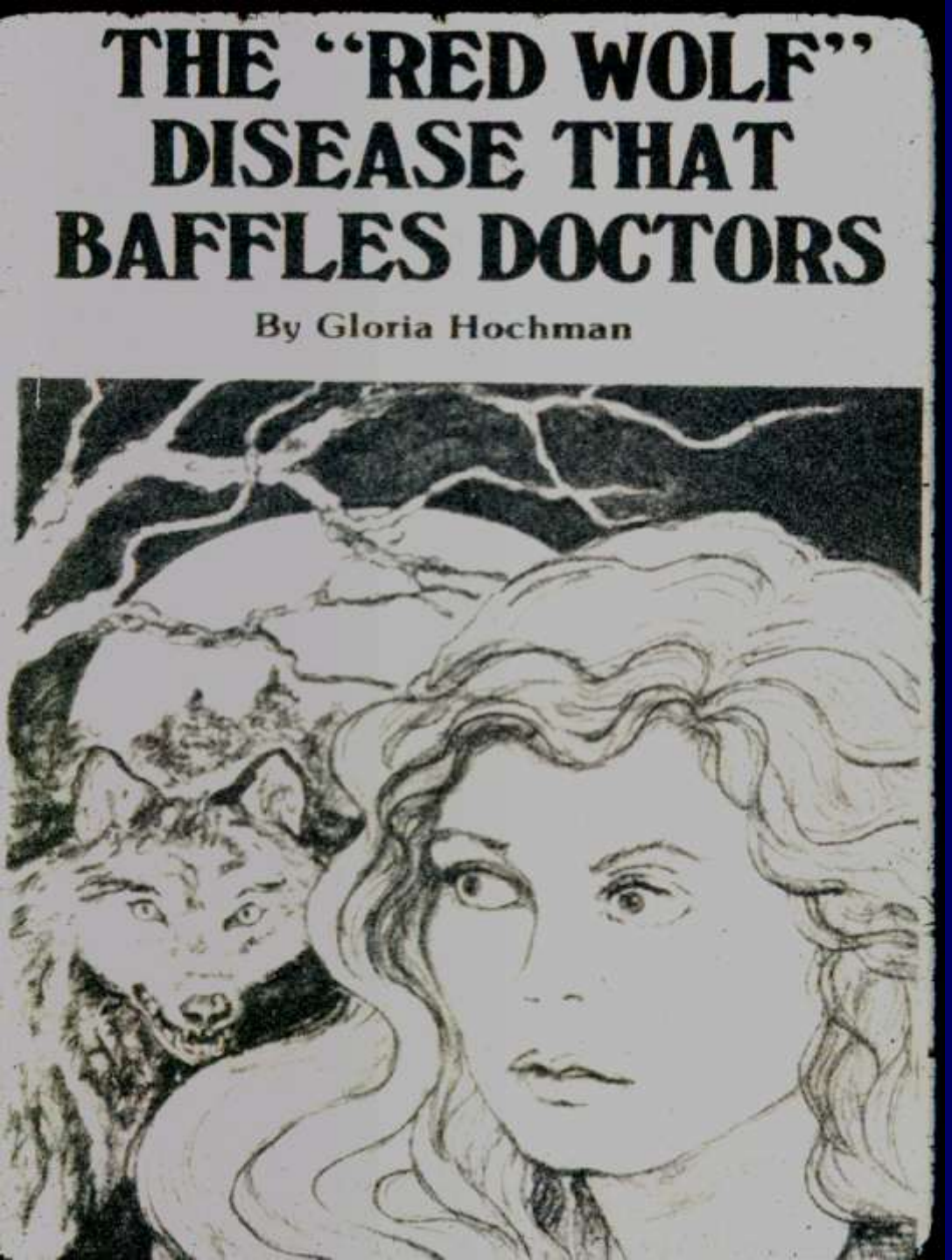
- **Genetic**
- **Environmental triggers**
- **Gender/hormonal factors**
- **Defective immune regulation**

# AUTO-IMMUNE DISEASES

- Failure of Self Recogntion
- **Failure of Self Tolerance**
- **TOLERANCE**
  - CENTRAL (Death of self reactive lymphocytes)
  - PERIPHERAL (anergy, suppression by T-cells, deletion by apoptosis, sequestration (Ag masking))
- Strong Genetic Predisposation
- Often Related To Other Autoimmune Diseases
- Often Triggerd By Infection

# Autoimmune Disease Characteristics

- remissions and exacerbations
- organ specific or organ non-specific
- persistence of antigen due to lack of clearance
- tissue damage is produced by:
    - antigen specific cytotoxic T cells (CD8+)
    - antigen-non-specific NK cells and macrophages
    - immune complexes
    - autoantibodies , and/or
    - granulocytes




# Systemic Lupus Erythematosus (SLE)

# Why is lupus such a mystery to us?

- Unlike many other autoimmune diseases, it affects many organs with varying disease manifestations over time.
- This makes it difficult to diagnose: average is 4 years and 3 different doctors
- There are all those antibodies to know…
- Treatments are OLD with significant side effects

# DEFINITION AND PREVALENCE

- Systemic lupus erythematosus (SLE) is a disease of unknown etiology in which tissues and cells are damaged by pathogenic autoantibodies and immune complexes
- Ninety percent of cases are in women

# *Who Gets Lupus?*

**Females > Males 7:1**

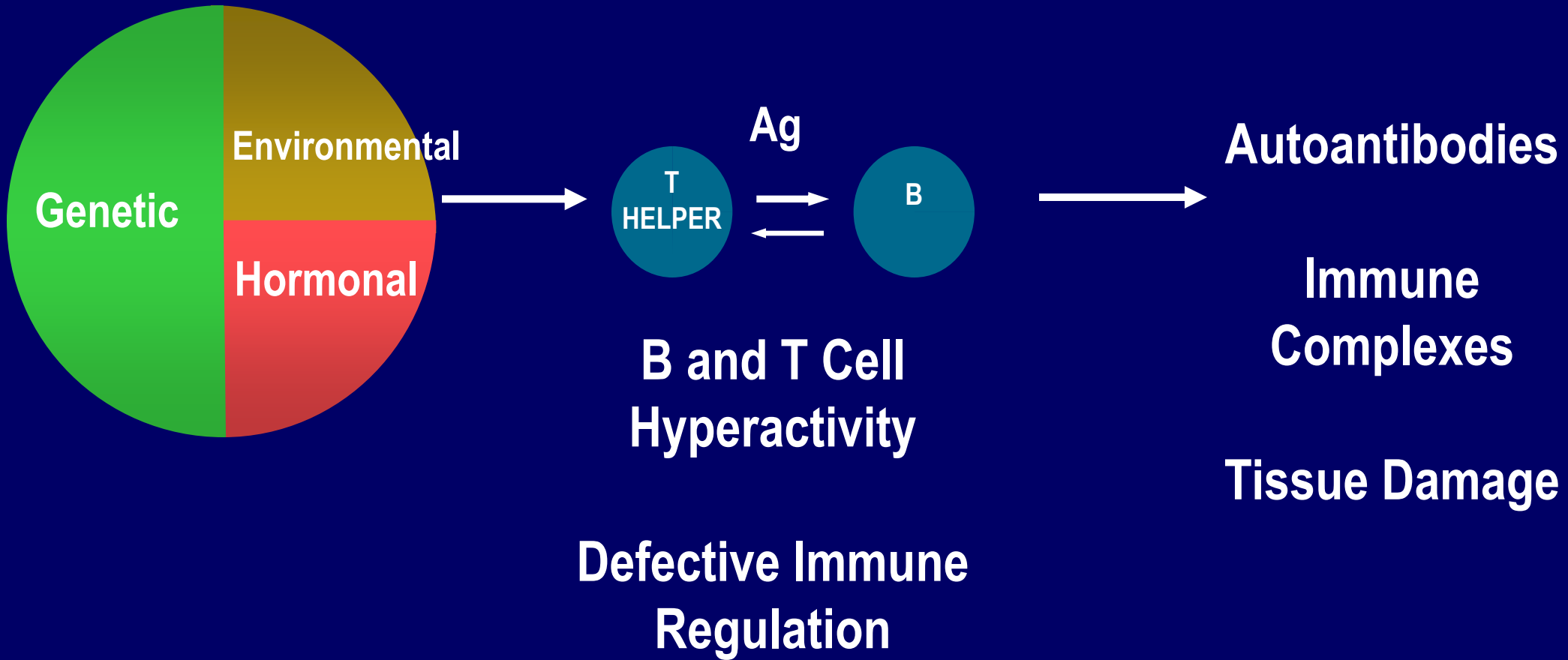
- **Childbearing 12:1**
- **Children, elderly 2:1**

**African-American (3-4x) > Caucasian**
**Asian**
**Hispanic**

# Etiology

- The etiology of SLE remains unknown. A genetic predisposition, sex hormones, and environmental trigger(s) likely result in the disordered immune response that typifies the disease.

# Pathogenesis of SLE



# *1-Observations to Support Genetic Factors in Lupus*

**1. Clustering in families**

**2. Concordance**

**- monozygotic (identical twins) 25-30%**

**- dizygotic 5%**

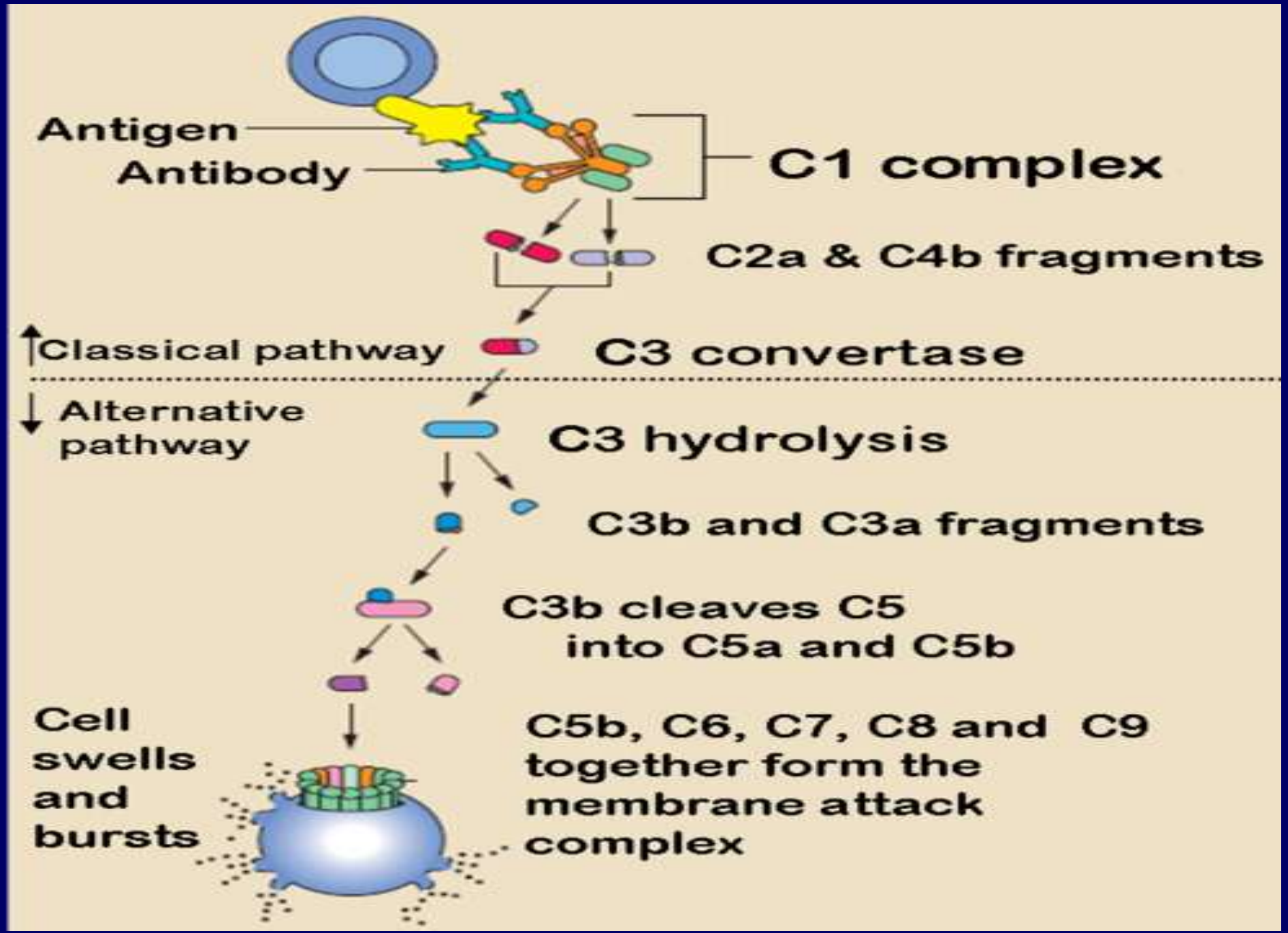
**3. Other autoimmune conditions in family members**

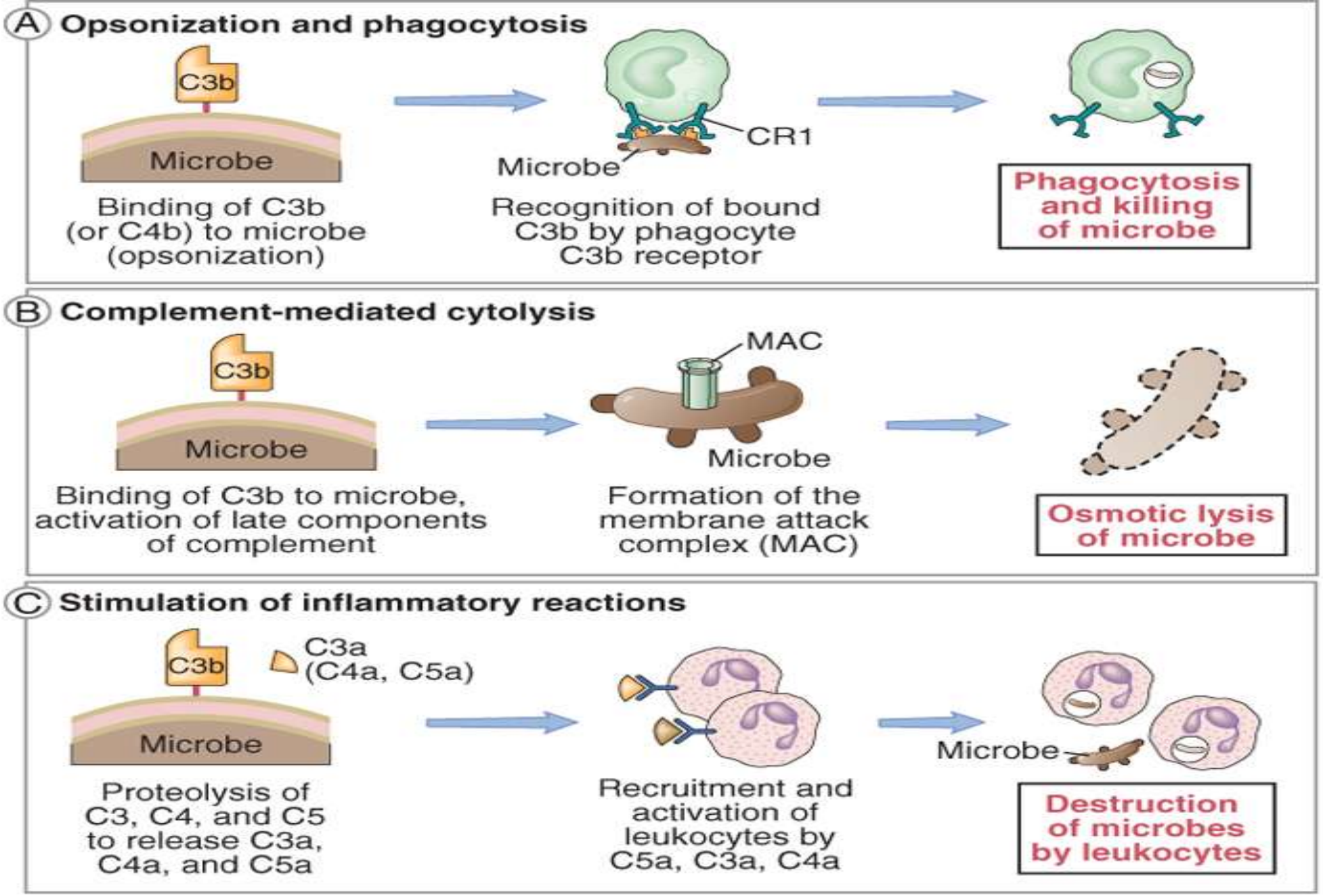
# Mode of Inheritance

**Polygenic (>95%) vs Monogenic (<5%)**

**Homozygous deficiency of:**

| | |
|---|---|
| C1q | (93%) |
| C4 | (88%) |
| C2 | (58%) |


Antigen
Antibody
C1 complex
C2a & C4b fragments
Classical pathway
C3 convertase
Alternative pathway
C3 hydrolysis
C3b and C3a fragments
C3b cleaves C5 into C5a and C5b
Cell swells and bursts
C5b, C6, C7, C8 and C9 together form the membrane attack complex



# *Paradox*

**Complement activation plays a critical role in the inflammatory process and tissue damage in SLE, but early complement deficiencies cause SLE.**

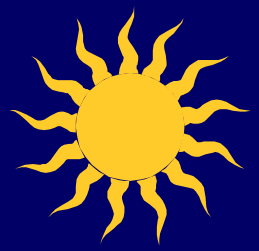
# *Possible Explanations*

1. C1q clears immune complexes

2. C1q binds to and clears apoptotic blebs (sources of autoantigens)

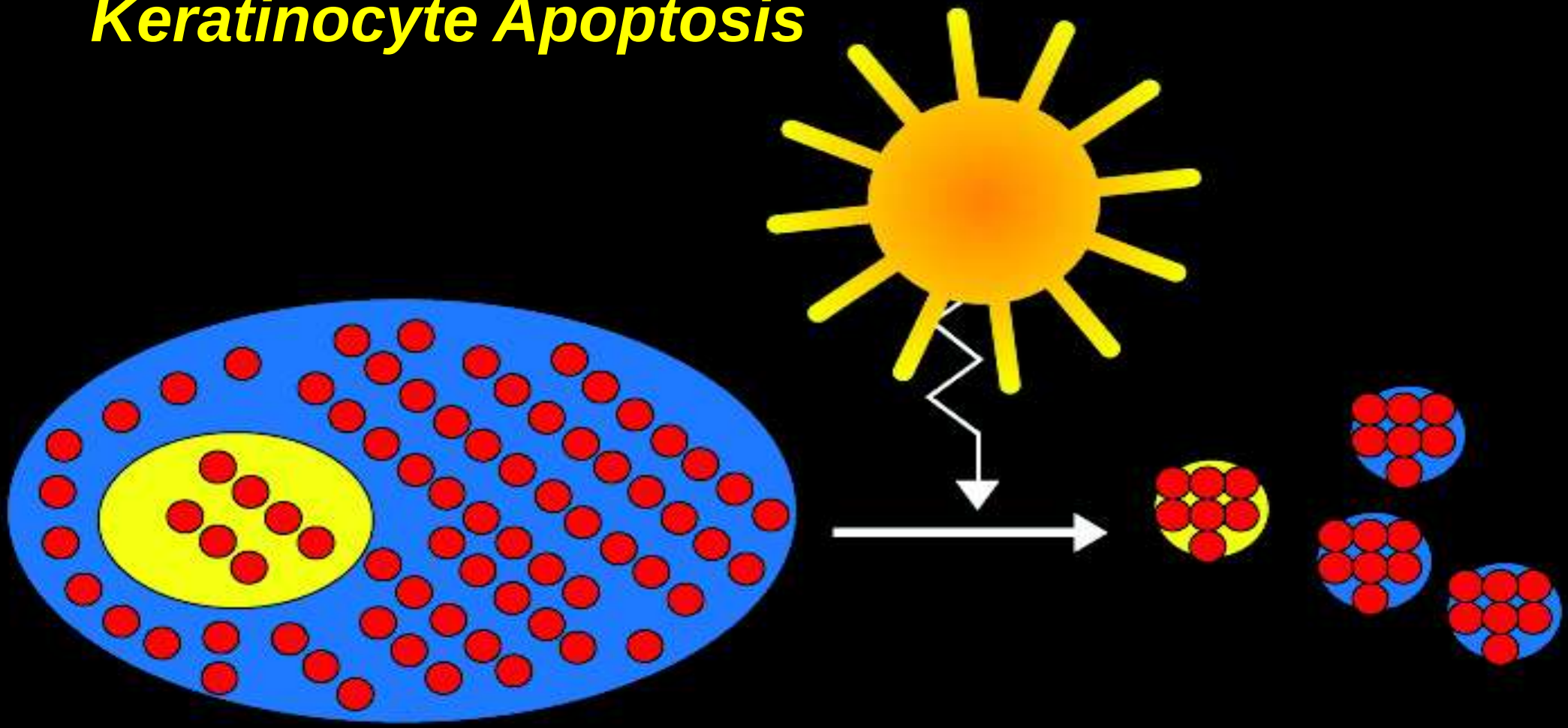
3. Absence of C1q permits sustained infections that could trigger autoimmune response.

# *2-Environmental Triggers*

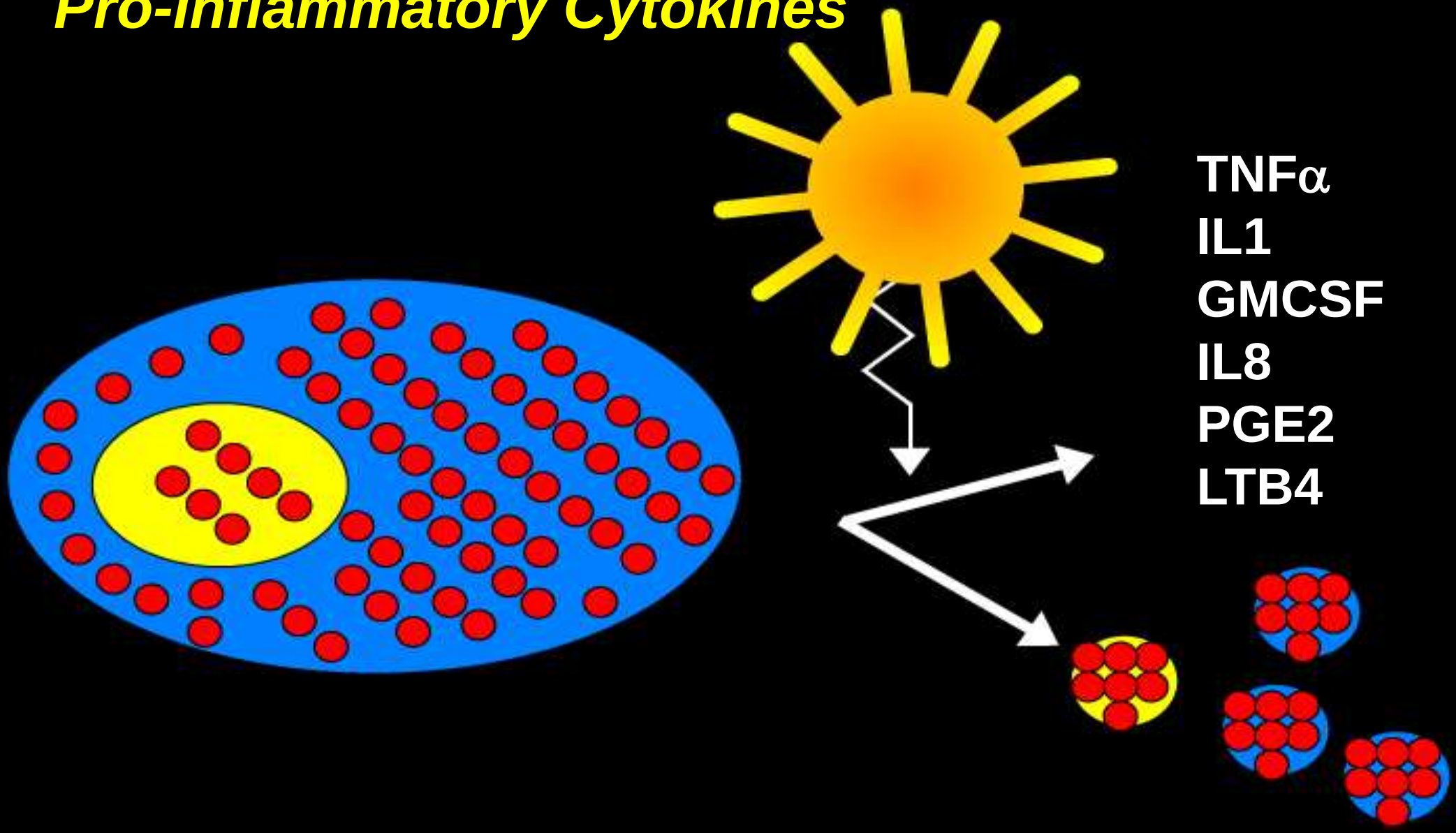


- **Ultraviolet light (photosensitivity)**
- **Drug-induced lupus**
  **milder, male =female, older ages**
- **Infectious agents (EBV, CMV)**

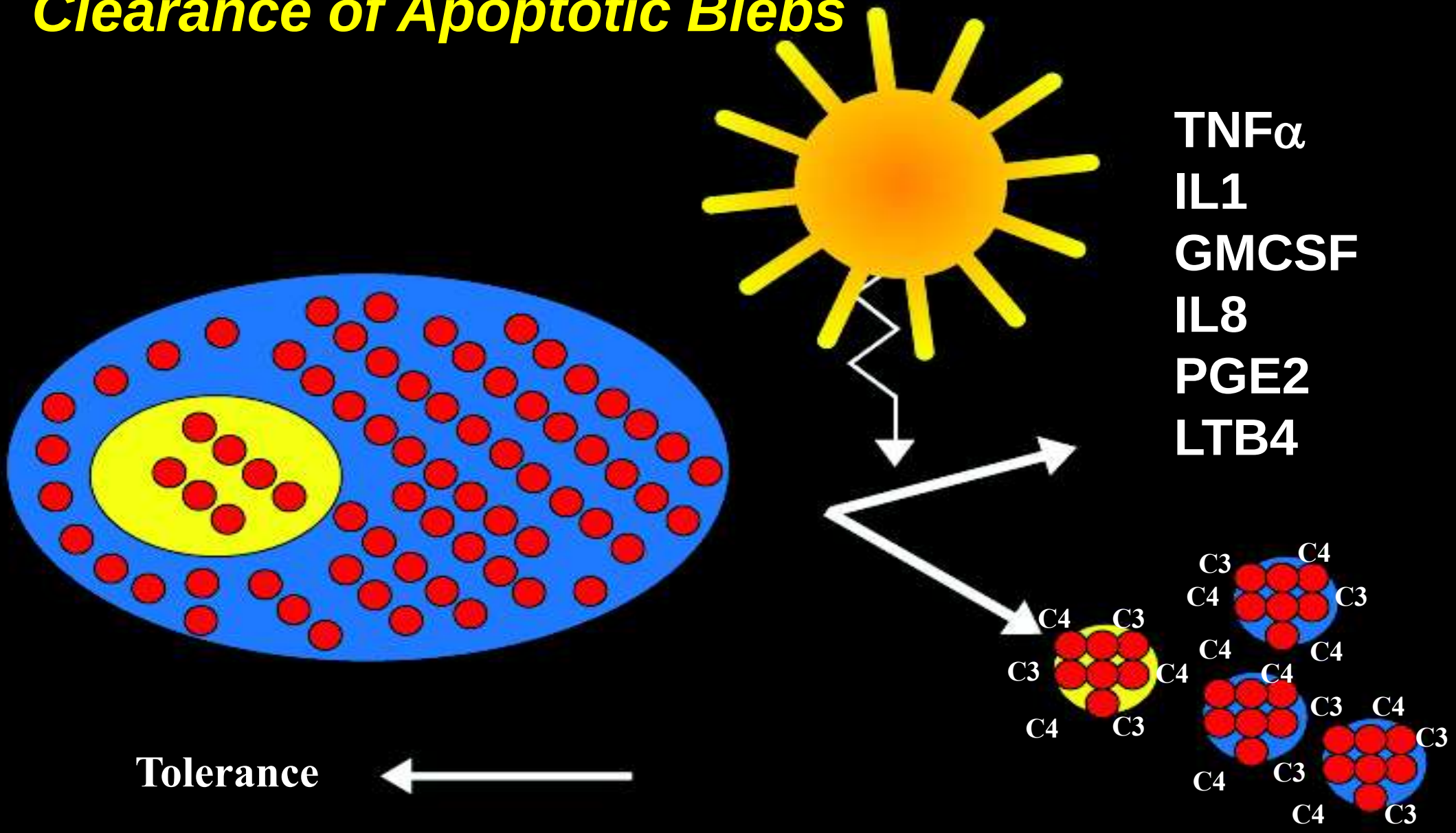
# *Ultraviolet Irradiation Induces Keratinocyte Apoptosis*



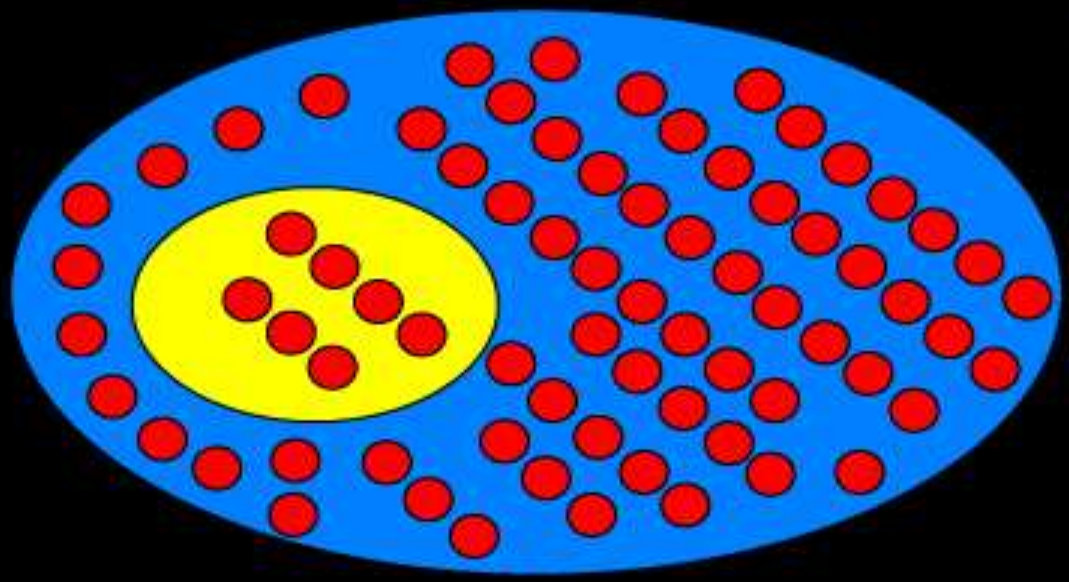
# *Ultraviolet Irradiation Induces Pro-Inflammatory Cytokines*

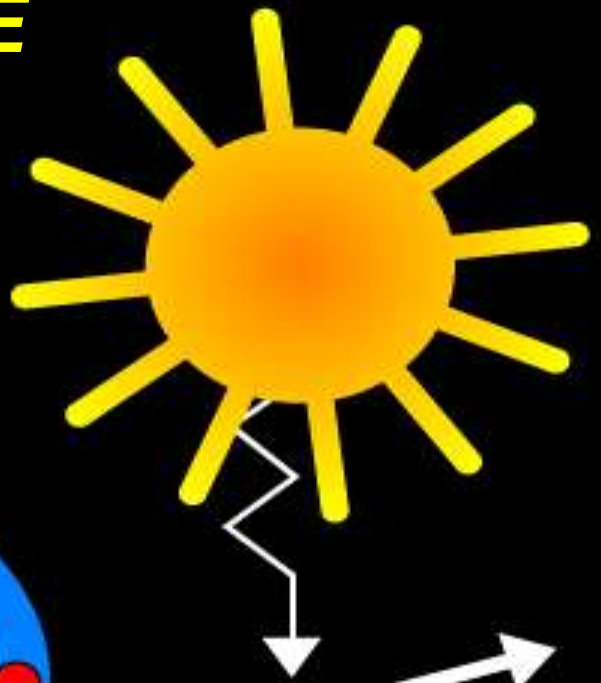


# *Complement Mediates Clearance of Apoptotic Blebs*

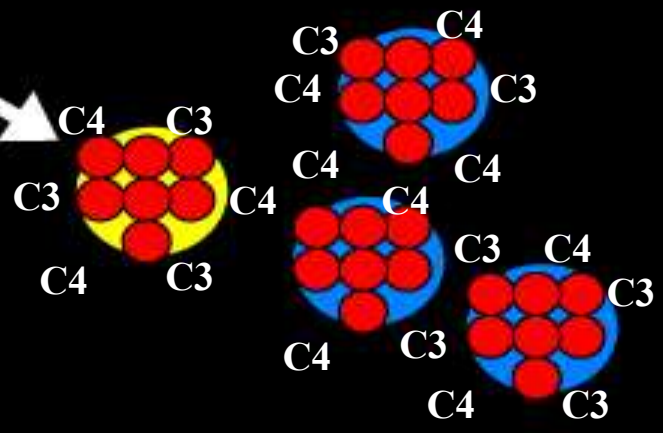


# *Impaired Clearance of Apoptotic Blebs in SLE*





**TNFα**
**IL1**
**GMCSF**
**IL8**
**PGE2**
**LTB4**




**Auto-Antibody**

**Lymph Nodes**
**Spleen**

# 3-Sex hormones

- Female : Male=7:1
- The sex difference is most prominent during the female reproductive years.
- In mice, castrating females and /or providing androgens or antiestrogens protects from disease,whereas castrating males and providing estrogens accelerates and worsens SLE.

- The metabolism of sex hormone is abnormal in some lupus patients. Men and women with lupus metabolized testosterone more rapidly than normal, and estrogenic metabolites of estradial persist longer in women.

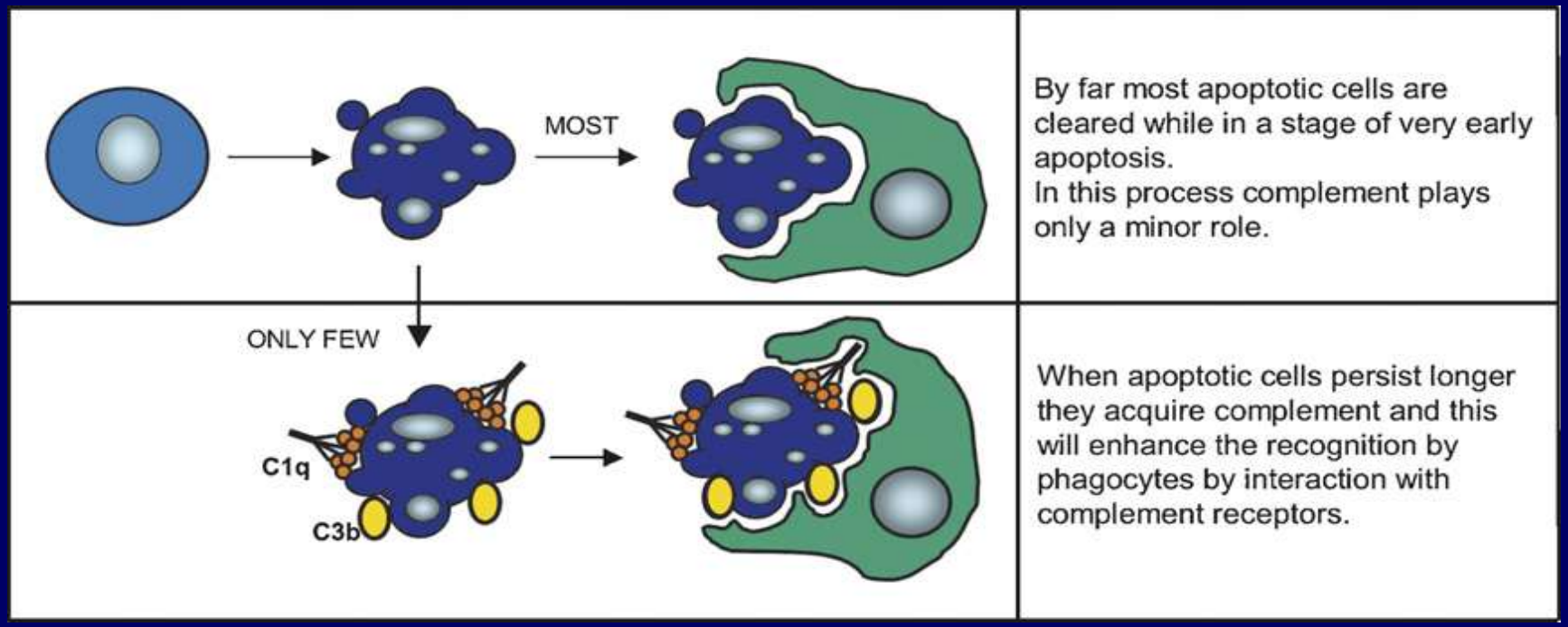
- Neuroendocrine system. Hyperprolactinemia, abnormalities in hypothalamic and/or pituitary function.

# 4-Immunologic Defects In Lupus

- Defective apoptosis
- IFN-α
- TLR signaling
- B-cell disregulation
- Pathology of autoantibodies

# *A-Defective clearance of apoptotic cells*

- *One common theme is defects in clearance of apoptotic cells resulting in autoantibody production*




  - *Phagocytes from lupus patients engulf far less during a 7 day period in vitro than phagocytes from healthy patients*

# *Defective clearance of apoptotic cells*

- Delayed or defective apoptosis then allows for prolonged exposure of intracellular antigens, “inflammatory cell death phenotype,” inflammatory cell recruitment and presentation of normally protected intracellular components as antigens allowing for autoantibody production

# Mechanism Summary

- Defects in clearance of apoptotic cells can lead to exposure of intracellular immunogenic components which can be taken up by DC and presented to autoreactive B cells).

- In the right genetic environment, these B cells may become activated to produce autoantibodies.

- Polymorphisms or mutations in genes in numerous steps of B-cell regulation or

  IFN-α responsiveness can predispose to SLE (FcγRIIa, IRF5, STAT4, BLK)

# Mechanism Summary

- Once autoantibodies (particularly anti-DS DNA) are present, they can complex with DNA exposed on dying cells and then bind to the FcγRIIa on PDCs, activate TLR 7 and 9, and result in high levels of IFN-α production.

- IFN-α encourages a feed-forward mechanism of continued plasma cell activation to produce increased amounts of autoantibodies and encourage further disease progression and tissue destruction.

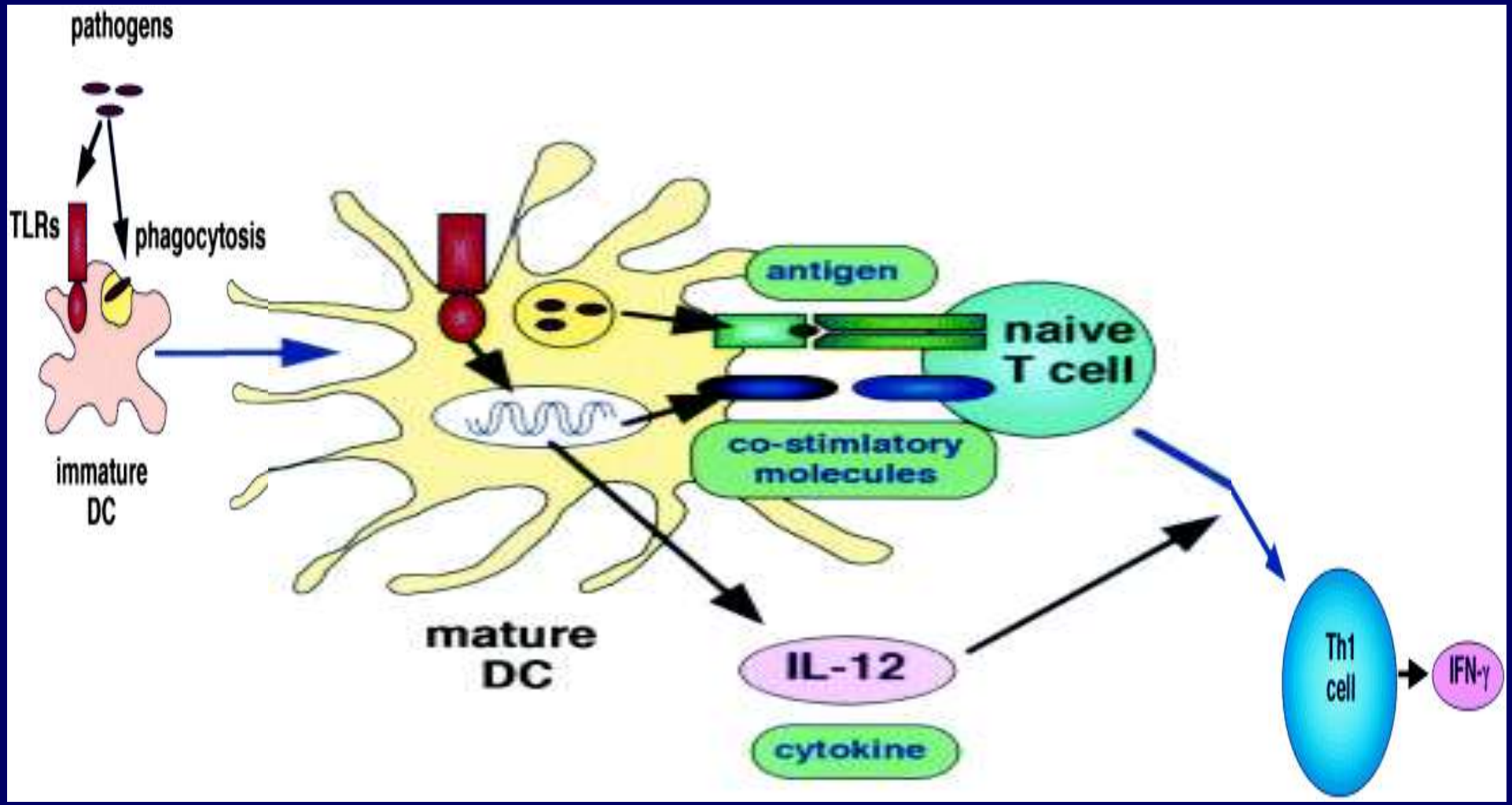
# *B-The importance of IFN-α*

- IFN-α is able to activate APCs after uptake of self material as well as promote B cell differentiation into plasma cells
- IFN-α levels appear to correlate with disease severity and levels of anti-DS DNA in SLE
- Patients with non-autoimmune diseases treated with IFN-α can develop positive ANA, anti-DS DNA abs and occasionally SLE.
- Conditions that naturally increase IFN-α levels (sunburn, viral infections) can induce SLE flares.

- IFN-α regulated genes are expressed at higher levels in the blood of SLE patients
- Plasmacytoid DCs are the major producers of IFN-α. SLE patients have 50-100 fold fewer in circulation as they have migrated to lymph tissues where they remain activated
- SLE susceptibility polymorphism in STAT4 results in increased sensitivity to IFN-α signaling.

# *C-The Innate Immune System May Also Play a Role*

- Toll-Like Receptors recognize molecular patterns (double stranded RNA, DNA, LPS etc) in order to provide rapid response to invading pathogens. They use defined signaling pathways to result in production of inflammatory cytokines and initiate inflammatory reactions.
- TLR7 and 9 are selectively expressed on PDCs
- Regulation in endosomes may regulate control of NFκB vs. IRF7 activation in human plasmacytoid dendritic cells

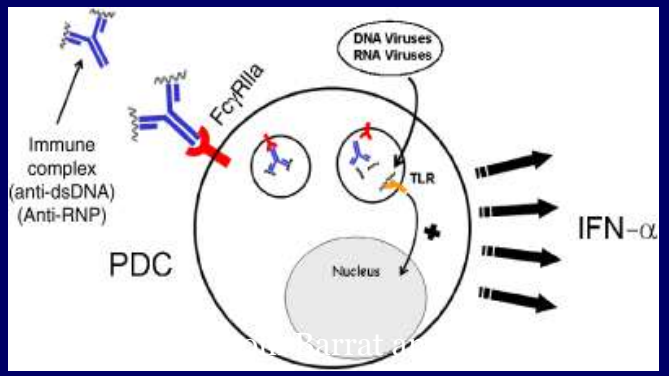

pathogens
TLRs
phagocytosis
immature DC
antigen
naive T cell
co-stimlatory molecules
mature DC
IL-12
cytokine
Th1 cell
IFN-γ

# *TLRs are thought to also recognize self antigens in the context of inflammatory diseases*

- All TLRs (except 5 and 10) have been shown to be activated by endogenous molecules in the context of cell death
- TLR7 and 9 are expressed only in endosomes to decrease the chance of coming in contact with endogenous RNA or DNA
- TLR7 and 9 are activated by DNA/anti-DNA IgG complexes resulting in IFN-α and autoantibody production.
- However, immune complexes are taken up by cells with FcγRIIa and taken to the endosome where they can activate TLR 7 and 9. This Results in

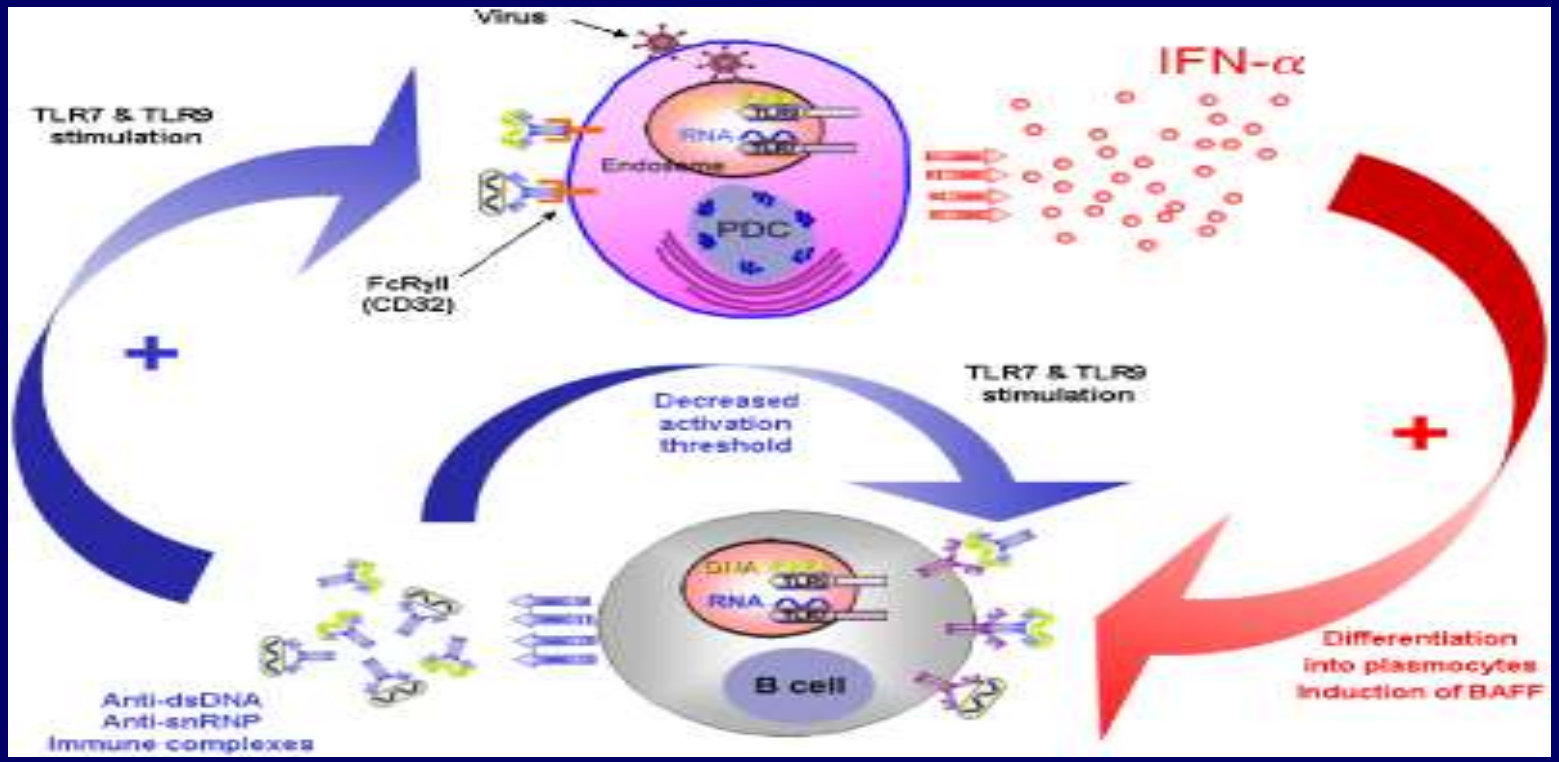
  signaling cascade activation that

  increases production of IFN-α.



# *D-B-cell Disregulation*

***This contributes to the disregulation of the B-cell: increased levels of IFN-α differentiate B-cells into antibody-producing plasmocytes and upregulates B-cell survival factors such as BAFF.***




***Additionally, recent identification of a genetic linkage of an allele that suppresses B-lymphocyte***
***kinase levels in SLE emphasizes the importance of regulation of B cell proliferation and tolerance***

# *Defective Immune Regulation*

**B and T-cell hyperactivity**

**Increased production of pro-inflammatory cytokines**

**Decreased clearance of immune complexes**

**Increased expression of surface molecules that increase B/T- cell activation (CD40L)**

# *Defective Immune Regulation*

**B and T-cell hyperactivity**

**Sustained autoantigens/impaired clearance of apoptotic cells**

**Epitope spreading due to lack of “turn off”**

**Exaggerated intracellular response to activation**

# EPITOPE SPREADING

- ***Definition***
  Initial response to one self determinant (one peptide) could expand to involve additional determinants on the same molecule as well as additional self-proteins. It explains how a response to one cryptic epitope can mature into a full-blown autoimmune response
- ***Examples***
  - anti-Sm to U1RNP
  - anti Ro/SS-A to anti-La/SS-B – lead to lupus-like

# *Immunological abnormalities in SLE*

## *B cell / antibody / complement systems:*

-> increased numbers of plasma cells in the bone marrow and peripheral lymphoid tissues
-> limited repertoire of Ig genes used in autoantibodies -> antigen-driven-clonal expansion
-> progressive accumulation of somatic mutations in Ig genes used in autoantibodies (affinity maturation?)
-> marked accumulation of circulating immune complexes during acute flares
-> decreased clearance of immune complexes through Fc receptors and complement receptors (cause or effect of increased IC?)
-> decreased circulating C3/C4, increased split products such as C3a, C3d

## *T cell system:*

-> in some cases, anti-T cell antibodies -> T cell lymphopenia
-> generalized depression in cell mediated immunity
-> apparent oligoclonal expansion of pathogenic T cells

# *Sources of Autoantigens*

1. Apoptotic cells

2. Activated cells (antigens move to cell membrane)

3. Modification of proteins during apoptosis

4. Infectious agents

# *Sources of Autoantigens*

**4. Infectious agents**

- **molecular mimicry**
- **epitope spreading**
- **nonspecific activation of B/T cells**
- **infection induced apoptosis**

# Why are autoantibodies so bad?

- Renal disease
  - **IgA, IgM, IgG and complement deposition in the mesangium and subendothelial and subepithelial of the GBM that results in complement activation and recruitment of inflammatory cells that result in tissue destruction.**
    - **Cross reactivity of anti-DS DNA antibodies with α-actinin may also result in a direct focusing of complement activation**

- Skin disease
  - **Inflammation and breakdown of the dermal-epidermal junction.**
  - **UV exposure can worsen because it promotes apoptosis in the skin resulting in autoantibody binding and tissue injury via complement activation or inflammatory cell activation**
  - **Anti-Ro antibodies are associated with skin flares**

# Why are autoantibodies so bad?

- In the CNS, vasculitis is rare
  - **Anti-NMDA receptor antibodies may contribute to cerebral lupus phenotypes**
  - **See more microinfarcts and degeneration or proliferative changes in blood vessels, thought to be related to IC deposition**
- Antiphospholipid abs may contribute to thrombotic events anywhere in the body
  - **aPLs bind to endothelial cells, monocytes, neutrophils and platelets causing inflammation and procoagulant release**
  - **This process is dependent on complement activation**

# *Other pathogenic roles of auto-Ab in SLE*

Anti-red cell and anti-platelets Abs -> hemolytic anemia, thrombocytopenia

Anti-cardiolipin antibodies -> miscarriages, vascular thrombosis

Anti-T cell antibodies -> immune dysfunction?

# ANA Fluorescence Patterns and Disease Association

| Nuclear Fluorescence Pattern | Disease Association |
|---|---|
| Rim (peripheral) | SLE |
| Homogeneous (diffuse) | Drug-induced LE, SLE |
| Speckled | SLE, Sjogren's, scleroderma |
| Nucleolar | Scleroderma |

-> 95% of SLE patients are ANA positive, thus a negative result virtually excludes SLE

-> but ANA can also found in other autoimmune diseases and chronic infections, thus a positive result cannot be the sole basis for diagnosis

# Summary

- Lupus is a disease of autoantibody formation that results in varied clinical manifestations
- Disregulation of apoptosis, B-cell survival and proliferation and IFN-α production appear to be the major inciting events
- Ongoing research into the mechanisms which lead to SLE will hopefully provide us with novel effective therapies with improved side effect profiles

*THANK YOU*